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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,143	CHRISTMANN, LEANDRO	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-3-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-82 have been canceled. Claims 83-118 have been added.

Claim Rejections - 35 USC § 112

New Matter

Claims 21 and 36-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The previous new matter rejections have been withdrawn because the claims have been canceled.

Applicants point to pg 8, lines 8 and 9, for support for the term "viewing". However, pg 8, lines 6-12, state "Figs. 2A - 2C illustrate the positioning of a micropipette made according to the present invention. Fig.2A shows the micropipette positioned over the vitelline membrane of an avian ovum and over the underlying germinal disk. Fig. 2B illustrates the indentation of the vitelline membrane of an avian ovum by depressing a micropipette. Fig. 2C illustrates the insertion of a micropipette into the germinal disk of a membrane avian ovum after penetrating the overlying vitelline." Nowhere does the citation discuss viewing or monitoring.

The phrase "viewing the surface of a germinal disc at an oblique angle to the surface of the germinal disc" in claim 83 has support on pg 23, 1st full ¶, taken with pg 25, lines 11-14, and Fig. 1.

The phrase "viewing a germinal disc at an angle not perpendicular to the base of the germinal disc" is new matter. Support for the scope claimed cannot be found in the dictionary definition of "oblique" because the definition has four options as cited by applicants. The specification does not clarify the definition of oblique is limited to "not perpendicular to the base of the germinal disc" as newly claimed.

The phrase "perpendicular axis of a germinal disc" in claim 107 is new matter. Support for the phrase cannot be found in Fig. 1. Fig. 1 shows viewing the object using the optical microscope by viewing the optical axis (6) at an oblique angle (see the eye looking in the optical microscope). Fig. 1 also shows viewing the object using the monitor positioned at an oblique angle relative to the surface of the germinal disc. Fig. 1 does not contemplate the broad scope encompassed by the phrase of viewing the optical axis at an oblique angle to any perpendicular axis of the germinal disc. Since the surface of the germinal disc is rounded, the perpendicular axis of a germinal disc is not limited to the optical axis (6) in Fig. 1. On the outer edge of the germinal disc as it sits on the microscope objective, the surface is at an angle and not parallel to the surface of the microscope. Therefore, a "perpendicular axis to the germinal disc" includes any axis that is perpendicular to any point on the surface of the germinal disc. The specification does not contemplate viewing any perpendicular axis to the germinal

disc at an oblique angle other than viewing the optical axis of the germinal disc at an oblique angle.

The phrase "injecting a nucleic acid sequence into the germinal disc by a micropipette" in claims 83, 97 and 107 has support on pg 25, line 15, through pg 26, line 3, taken with pg 27, lines 10-15.

The phrase "injecting a nucleic acid sequence into the avian embryo using the micropipette" in claim 117 has support on pg 25, line 15, through pg 26, line 3, taken with pg 27, lines 10-15.

The phrase "allowing the germinal disc to develop into a chick" in claims 83, 97 and 107 has support on pg 27, lines 10-15.

The phrase "allowing the avian embryo to develop into a transgenic avian" in claim 117 has support on pg 27, lines 10-15.

The phrase "providing a microscope having an objective, a micropipette, a monitoring unit and a chicken embryo wherein the optical axis of the monitoring unit is at an oblique angle to the optical axis of the objective", in claim 117 is supported in Fig. 1 (62 (optical axis of the monitoring unit) and 6 (optical axis of the objective) taken with page 23, lines 3 to 6, and page 25, line 11.

The limitation of chicken in claims 84, 91, 98, 103, 108, 113 and 118 is found on pg 29, line 14.

The limitation of light microscope in claim 85 is found on pg 21, lines 1-2.

The phrase "wherein the germinal disc is placed in a light beam" in claims 86, 99 and 109 is new matter. No support can be found for the phrase and none has been provided.

The phrase "oscillation is applied to the micropipette" in claims 87, 100 and 110 is new matter. No support can be found for the claim and none has been provided.

The terms "vector" and "non-viral vector" in claims 88, 89, 101 and 111 can be found on pg 27, line 12.

The term "plasmid" in claims 90, 102 and 112 is new matter. No support can be found for the claim and none has been provided.

The phrase "delivering the germinal disc to a recipient avian female" in claims 92, 104 and 114 does not have support as broadly claimed. The phrase encompasses injecting the germinal disc anywhere into the female, which is not described in the specification as originally filed. No support can be found for the phrase and none has been provided.

The phrase "delivering is to an infundibulum of the recipient avian female" in claim 93 is found on pg 28, lines 6-9.

The phrase "wherein injecting a nucleic acid sequence into the germinal disc by the micropipette comprises inserting the micropipette into the germinal disc" in claim 94, 105 and 115 is new matter. No support can be found for the phrase and none has been provided.

The phrase "wherein inserting the micropipette into the germinal disc comprises penetrating a vitelline membrane" in claim 95 is new matter. No support can be found for the phrase and none has been provided.

The phrase "wherein the nucleic acid sequence is injected into a recipient cell of the germinal disc" in claims 96, 106 and 116 is new matter. No support can be found for the phrase and none has been provided.

Applicants are reminded that support for every claim must be provided for the response to be considered "fully responsive." In order to expedite prosecution, the examiner has provided support for the new claims for which applicants failed to provide support. Future responses that do not begin with a section describing support for each and every new phrase specifically by page and line number (with discussion as necessary) will be considered non-responsive.

Enablement

Claims 51-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a transgenic chicken by 1) providing i) an optical microscope having an objective, ii) a micropipette, iii) a monitoring unit and iv) a chicken embryo, wherein the optical axis of the monitoring unit (62, in Fig. 1, see pg 23, lines 3-6) is at an oblique angle to the optical axis of the objective (6, in Fig. 1, see pg 25, line 11), 2) injecting a nucleic acid sequence into the chicken embryo using the micropipette; and 3) allowing the chicken embryo to develop into a transgenic chicken

that is a germline chimera, does not reasonably provide enablement for making any species of transgenic avian or applying oscillation or piezo-electric oscillation to the micropipette used to deliver the nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The rejection of claims 51-82 under enablement has been withdrawn because the claims have been canceled.

The broad claims are directed toward delivering nucleic acid into an avian embryo to produce a transgenic avian. The only enabled purpose for the method is to obtain a transgenic avian that is a germline chimera, i.e. that carries the exogenous nucleic acid in its germ cells and passes the nucleic acid on to its offspring. The broad claims encompass delivering nucleic acids in the form of vector (plasmids, viral vectors), cells transfected with a vector or a donor nucleus. Methods of making transgenic chickens by injecting vectors or cells transfected with vectors into chicken embryos were known in the art:

PGCs had been isolated from chickens, transduced with retrovirus, and immediately injected into the vasculature of Stage 15 chick embryos to obtain germline transmission of a transgene (Vick, Proc. R. Soc. Lond., 1993, Vol. 251, pg 179-182). Plasmid DNA had been injected into the germinal disc of chick zygotes isolated before being laid to obtain germline transmission of a transgene (Love, of record, Bio/Technology, 1994, Vol. 12, pg 60-63). Retroviral vectors had been injected into the

subgerminal cavity of an avian embryo in a freshly laid egg to obtain germline transmission of a transgene (Thoroval, Transgenic Research, 1995, Vol. 4, pg 369-376). Retroviral vectors had been used to introduce a truncated antibody receptor into chickens "somatically" and express the receptor in the bursa at hatch (Sayegh, Dec. 15, 1999, Vol. 72, pg 31-37; pg 32, 2nd full ¶, lines 2-5 and 16-18; ¶ bridging pg 33-34).

The specification does not enable making any transgenic avian as broadly encompassed by claims 83, 97, 107 and 117. The specification summarizes methods of introducing a nucleic acid into chicken embryos known in the art (pg 3-5). The specification summarizes methods of obtaining transgenic mice known in the art at the time of filing (pg 2-3); however, methods of making transgenic mice do not correlate to making transgenic avians (Proudman of record, 2001, "The quest for transgenic poultry: birds are not mice with feathers" Biotechnology in Animal Husbandry, Vol. 5, Kluwer Academic Publishers, pg 283-299). The specification does not enable injecting obtaining any transgenic germline chimeric avian because the art at the time of filing was limited to using the method to obtain germline chimeric chickens. The specification does not correlate the structure of chicken embryos to any other avian embryos. The art did not teach obtaining a germline chimeric non-chicken avian. Without such guidance it would require one of skill undue experimentation to introduce a nucleic acid into any species of avian embryo such that a germline chimeric avian was obtained. The claims should be limited to chicken embryos, germinal discs of chicken embryos and transgenic chickens.

Applicants argue the specification taken with what was known in the art provides the practitioner of skill in the art with adequate guidance to produce transgenic avians other than chickens (pg 7, 2nd full ¶). Applicants' argument is not persuasive and ignores the attempts in the art to make transgenic avians other than chickens that failed. The facts set forth by the examiner do not allow one to reasonably come to the conclusion asserted by applicants. While the art taught a nucleic acid could be injected into any avian embryo, the only transgenics avians (which must be germline chimeras according to the instant application) made by injecting a nucleic acid into an embryo known in the art were chickens. The art described attempts to make non-chicken transgenic avians by injecting nucleic acids into non-chicken avian embryos, but the attempts failed to produce a transgenic non-chicken avian. The specification does not overcome the failures in the art to make non-chicken transgenic avians by providing any correlation between chickens and other avians or by teaching how to overcome the failures in the art. Thus, it is not readily apparent that any purported improvements in how the nucleic acid is injected would allow one of skill to overcome the unpredictability in the art and suddenly be able to inject a nucleic acid into any avian embryo and obtain a germline chimera. Without some indication that the problem with injecting a nucleic acid into any avian embryo and obtaining a germline chimera was the "optically opaque yolk underlying the oocyte or germinal disk", applicants' improvement would not be enough for one of skill to predictably inject a nucleic acid into any avian embryo to obtain any transgenic avian as broadly claimed.

Claims 87, 100 and 110 require using a micropipette that has an oscillator, specifically a piezo-electric oscillator, which was only used in the art of transgenics for delivering a donor nucleus (Dozortsev, of record, Zygote, May 1998, Vol. 6, No. 2, pg 143-147, and Korfiatis, of record, Cloning and Stem cells, 2001, Vol. 3, No. 3, pg 125-138, for example). Therefore, claims 87, 100 and 110 are limited to methods of delivering a donor nucleus to an avian embryo. Claims 87, 100 and 110 are not enabled because the specification does not enable delivering a donor nucleus to make a transgenic avian. The specification contemplates removing the nucleus of an avian egg (pg 37, Example 3) and transplanting a donor nucleus into the egg (pg 39, Examples 5 and 6), i.e. cloning. The art at the time of filing did not teach how to clone avians. Therefore, it was unpredictable how to clone avians at the time of filing. The specification does not teach obtaining a viable offspring by delivering a donor nucleus. The specification does not adequately correlate methods known in the art capable of cloning to the method of microinjection described in the specification. The specification does not correlate the structure of mammalian embryos capable of cloning known in the art to avians embryos such that one of skill could use mammalian cloning methods to clone avians. Without such guidance it would require one of skill undue experimentation to microinject a donor nucleus using oscillation to make transgenic avians that carry the donor nucleus. Therefore, claims 54, 55, 67 and 76 are not enabled as they relate to using oscillation to deliver a donor nucleus to make a transgenic avian.

Applicants argue an oscillator is not limited to producing a cloned avian. Applicants argue the purpose of applying oscillation is to assist the bevel (the tip) of the micropipette (e.g., needle) through the cell membrane. Without the oscillation, applicants state the tip of the micropipette may produce an invagination in the membrane leading to a snapback of the membrane once the bevel punctures the invaginated membrane. Such a snapback of the membrane may lead to the micropipette tip ending up deep inside of the cell producing disruption and inactivation of the cell. Applicants conclude that the rejection should be withdrawn because the oscillator is not limited to the production of cloned avians. Applicants' arguments are not persuasive. Applicants have not addressed why one of skill would use oscillation for purposes other than microinjecting a donor nucleus – the only use in the art or in the specification for applying oscillation while using a micropipette.

Indefiniteness

Claims 83-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 51-82 has been withdrawn because the claims have been canceled.

Claim 83 is indefinite because the preamble is limited to a transgenic avian while the body of the claim encompasses using any species of "germinal disc".

Claim 83 is indefinite because the preamble is limited to a transgenic avian while the body of the claim is limited to developing a germinal disc into a chick.

Claim 83 is indefinite because the body of the claim is limited to developing the germinal disc into a chick while producing any species of transgenic avian.

The phrase "the microscope..." in claim 85 lacks antecedent basis.

The phrase "the delivering..." in claim 93 lacks antecedent basis.

The phrase "wherein inserting the micropipette into the germinal disc" in claim 95 lacks antecedent basis.

Claim 97 is indefinite because the preamble is limited to a transgenic avian while the body of the claim encompasses using any species of "germinal disc".

Claim 97 is indefinite because the preamble is limited to a transgenic avian while the body of the claim is limited to developing a germinal disc into a chick.

Claim 97 is indefinite because the body of the claim is limited to developing a germinal disc into a chick while producing any species of transgenic avian.

The phrase "viewing a germinal disc at an angle not perpendicular to the base of the germinal disc" in claim 97 is indefinite. The scope encompassed by the phrase cannot be determined. The metes and bounds of the "base of the germinal disc" cannot be determined, thus "perpendicular to the base of the germinal disc" cannot be determined, and thus "not perpendicular to the base of the germinal disc" cannot be determined. The metes and bounds of the claim cannot be found in the dictionary definition of "oblique" because the definition has four options with four different scopes.

The specification does not clarify the metes and bounds of "not perpendicular to the base of the germinal disc" as newly claimed.

The phrase "perpendicular axis of a germinal disc" in claim 107 is indefinite. Fig. 1 shows viewing the object using the optical microscope by viewing the optical axis (6) at an oblique angle (see the eye looking in the optical microscope). Fig. 1 also shows viewing the object using the monitor positioned at an oblique angle relative to the surface of the germinal disc. It is unclear if the phrase is limited to the optical axis shown in Fig. 1 (6) or if the phrase is intended to encompass any axis that is perpendicular to any surface of the germinal disc.

Claim 117 is indefinite because the preamble is limited to a transgenic avian while the body of the claim is limited to using a chicken embryo.

Claim 117 is indefinite because the body of the claim is limited to using chicken embryo while injecting an avian embryo and developing into any species of transgenic avian. The phrase "the avian embryo" in claim 117 lacks antecedent basis.

Claim Rejections - 35 USC § 103

The rejection of claims 51-82 under obviousness has been withdrawn because the claims have been canceled.

New claims 83-118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka (1994, J. Reprod. Fert., Vol. 100, pg 447-449) in view of Sang (Molecular Reproduction and Development, 1989, Vol. 1, pg 98-106).

Tanaka (1994, J. Reprod. Fert., Vol. 100, pg 447-449) taught delivering a chicken embryo into the birth canal of a hen and allowing the embryo to become a chick (pg 447, col. 2, "Materials and Methods;" pg 448, Fig. 1; pg 448, col. 1, line 4; pg 448, col. 2, 1st full ¶, line 9). Tanaka taught delivering a linearized nucleic acid sequence encoding MiwZ to the embryo before delivering the embryo to the recipient hen (pg 449, col. 1, last ¶). Tanaka did not teach delivering the DNA into the germinal disc of embryo with a micropipette as claimed.

However, Sang (Molecular Reproduction and Development, 1989, Vol. 1, pg 98-106) taught delivering plasmid DNA to the germinal disc of a chicken embryo using a micropipette held in a micromanipulator and allowing the embryo to develop into a chick (pg 99, col. 1). Sang determined the injection was a depth of 140-200 μm beneath the vitelline membrane (pg 99, col. 1, 2nd full ¶, 1st sentence); therefore, the embryo inherently was viewed at an oblique angle to the surface of the germinal disc of the embryo as in claim 83. To make a determination of the injection depth, the embryo must have been viewed from the side. Claims 97 and 107 are included because the "viewing" step is indefinite. The micropipette held in a micromanipulator taught by Sang on pg 99, col. 1, 2nd full ¶ inherently had a light microscope because a micromanipulator is an attachment for a light microscope (see definitions of "micromanipulator" by Dorlands Medical Dictionary and by Drug Discovery and Development of record). Therefore, the embryo was in a beam of light as in claims 86, 99 and 109

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to deliver DNA to an embryo, deliver the embryo into a recipient

female and allow the embryo to become a chick as taught by Tanaka wherein the DNA was injected into the germinal disc of the embryo using the micromanipulator taught by Sang. One of ordinary skill in the art at the time the invention was made would have been motivated to deliver the DNA of Tanaka using the micromanipulator taught by Sang because Sang had increased survival rate as compared to Tanaka (pg 100, lines 5-8, Table 1, of Sang (40%) as compared to the last ¶ of Tanaka (6 out of 20=30% or 3 out of 20=15%). One of ordinary skill in the art would have been motivated to replace the one-cell embryo of Tanaka with the embryo having a germinal disc taught by Sang to increase the number of cells receiving the DNA and to increase the survival rate of the embryos as described by Sang.

Thus, Applicants' claimed invention, as a whole is prima facie obvious in the absence of evidence to the contrary.

Applicants argue none of the references viewed the embryo as claimed. Applicants' argument is not persuasive and has been addressed above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER